***Complementary Medicines Australia*** *submission to the TGA consultation: Proposed changes to the Permissible Ingredients Determination - low-negligible risk.*

**6 October 2020**

**To:**
Complementary and OTC Medicines Branch
Therapeutic Goods Administration
PO Box 100 Woden
ACT 2606
complementary.medicines@health.gov.au

**From:**
Complementary Medicines Australia
PO Box 450 Mawson
ACT 2607

Telephone: 02 6260 4022
Facsimile: 02 6260 4122
E-mail: technical@cmaustralia.org.au
Website: cmaustralia.org.au

# Contents

# Complementary Medicines Australia Response to the Proposed changes to the Permissible Ingredients Determination Consultation

Complementary Medicines Australia (CMA) welcomes the opportunity to respond to suggested requirements via the Permissible Ingredients Determination Consultation: annual changes 2020-21.

CMA is the peak body of the complementary medicines sector, representing greater than 80% of the sector by sales of complementary medicines. Our members include stakeholders across the value chain, including manufacturers, raw material suppliers, distributors, consultants, retailers, and allied health professionals. The sector has evolved into a globally recognised and respected industry helping to grow the Australian export economy, supporting increasing numbers of domestic skilled jobs in innovation, research, and manufacturing.

CMA is committed to a vital and sustainable complementary medicines sector. We support safe but appropriate and balanced risk-based regulation of complementary medicines and health products. The sector in Australia provides health enhancement and preventative health strategies to help Australians live healthier lives and in turn, to reduce the burden on the healthcare system wherever possible.

The complementary medicines industry supports regulation of complementary healthcare products that is commensurate with the low level of risk these products represent within the context of 'Light Touch, Right Touch'[1] approach to regulation that is consistent with the principles of Government regulation and guidance for policy-makers to take a conservative and balanced approach to regulating by reducing burden wherever possible and avoiding regulation where it is not necessary. We seek appropriate levels of regulation to ensure high quality products whilst seeking streamlined systems that are not overregulated and are able to provide appropriate and competitive access to innovative health products sought by Australian and international consumers.

In relation to some of the existing proposals and relevant changes to the Determination, it is evident that there is disparity between the suggested approaches to substances to that of comparable overseas regulators and research organisations and even comparable Australian Government agencies. Disparity without appropriate cause between product categories and regulators has caused problems in the past for consumers and industry. The Australian community generally do not seek increased complexity and difference in rules but increased harmonisation across product categories and agencies where possible to enable simplicity, reduce confusion, and minimise red tape.

[1]CMA (2014). Light Touch, Right touch for Complementary Medicines [Report]

## Easily dissociable magnesium salts

***Consultation - Proposed specific requirements for the specified list of magnesium salts:***
*Magnesium is a mandatory component of this ingredient.*
*When used in medicines:*

a. *with an oral route of administration;*
b. *not indicated for laxative (or related) use; and*
c. *the maximum recommended daily dose for:*
    i. *children aged between 1 and 3 years (inclusive) provides 65 mg or more total magnesium;*
    ii. *children aged between 4 and 8 years (inclusive) provides 110 mg or more total magnesium; or*
    iii. *individuals aged 9 years or older provides 250 mg or more total magnesium;*

*the following warning statements are required on the label:*

- *'This product may have a laxative effect. Discontinue use if you develop diarrhoea (or words to that effect)'.*

*When used in medicines with an oral route of administration, the following warning statement is required on the label:*

- *'Not suitable for infants under the age of twelve months' (or words to that effect).'*

The TGA is proposing to include new laxative-based warning statements for listed medicines that are not already indicated for laxative use (which include other warnings per the Permissible Indications Determination) where those medicines contain higher doses of easily dissociable magnesium salts (>250mg) due to possible osmotic laxative effects. This is considered a very conservative level in comparison to the already conservative level of 350mg identified by comparable organisations, and is based on doses of up to 250 mg elemental magnesium per day being at the level of no adverse effect and due to the concern that magnesium-containing supplements could be taken simultaneously.

Based on the available evidence, the proposed warning statement is not commensurate with the risk posed for magnesium supplements containing >250mg of magnesium and to apply a blanket statement to products containing >250mg of magnesium would not be the best regulatory practice approach. The osmotic laxative effect of orally ingested magnesium is almost always associated with supplemental doses of magnesium (≥ 360 mg elemental magnesium per day) from dietary supplements/medicines. In addition, the generalisation of all magnesium types under 'easily dissociable magnesium salts' to which the warning statement would apply, requires further consideration, as it is widely accepted that particular types of magnesium are more likely to provoke an osmotic effect than others.

Further, the anticipation that the simultaneous consumption of magnesium-containing supplements and associated laxative effects is sufficient to warrant the warning statement for products containing >250mg is unjustified and does not align with the 'real-world' occurrence of Adverse Drug Reactions (ADRs) associated with simultaneous ingestion of magnesium supplements, nor with the common practice of magnesium supplementation by consumers and recommendations by health professionals. These ideas are further explored below.

**Warning statement ≥250mg**

The literature supporting the proposed specific requirement, which requires a warning statement on magnesium products which provide 250 mg or more total magnesium in individuals aged nine years or older, appears to be based on the European Scientific Committee on Food (SCF) (SCF 2006), which does not categorically support these findings. Moreover, the proposed specific requirement is inconsistent with the recommendations of comparable regulatory bodies and research organisations, such as the Norwegian Scientific Committee for Food and Environment (VKM) (VKM, 2016), the Institute of Medicine's (IOM) (IOM, 1997) and Australia's own National Health and Medical research Council (NHMRC) (NHMRC, 2014).

The analysis of data summarised and presented by the SCF (2006), which included studies ranging from 1988-2001, found that mild diarrhoea occurs in only a small percentage of adult subjects at oral doses of about 360/365mg magnesium per day. The characterisation of risk provided by the SCF was that diarrhoea induced by easily dissociable magnesium salts or compounds like magnesium oxide, is completely reversible within one to two days and does not represent a significant health risk in normal subjects.

A more recent review of 13 studies including 10 randomised controlled trials, one open-labelled trial, one high-dose magnesium study and one meta-analysis by the VKM (2016) found that despite reports of an increased frequency of diarrhea in most studies, there was no significant difference between treatment group and placebo group in any of the studies, and one non-significant report of a higher frequency of gastrointestinal symptoms in the magnesium group compared with the control group. This review provided that the VKM (2016) were unable establish a no-adverse-effect-level (NOAEL) for magnesium since the critical endpoint (gastrointestinal symptoms) is mild and rapidly reversible. The VKM (2016) were also unable to identify the research reports referred to by the SCF (2006) constituting the basis for a NOAEL of 250mg/day. The review therefore, informed the VKM's advice of a safe upper limit of 350mg per day for magnesium salts in adults and is in harmonisation with the IOM approach (1997), which advises that 350mg supplementary magnesium per day for adults is not likely to pose

risks of adverse health effects in almost all individuals in the general population, based on the lowest-observed-adverse-effect level (LOAEL) for mild diarrhea, which is considered to be a very mild, rapidly reversible adverse effect of magnesium salts in food supplements.

Further, the United Kingdom Expert Group on Vitamins and Minerals (EVM) (2003) state that magnesium salts are used in food supplements at levels providing up to 750 mg/day and concluded that, although a small percentage of patients and healthy volunteers reported mild and reversible diarrhea, this effect was only observed in a limited number of studies at doses of between 384-470 mg/day. Diarrhoea was not observed in the majority of studies using similar or higher doses. The EVM also provide that for guidance purposes, 400mg/day supplemental magnesium would not be expected to result in any significant adverse effects.

The Natural Medicines Database (NMDB, 2020) also report very high levels of reliable clinical evidence, which confer the safe oral use of magnesium when used in doses up to the tolerable upper intake suggested level of 350 mg daily. The term, tolerable upper intake level, is intended to imply a level of intake that can, with high probability, be tolerated biologically and the level at which intake is unlikely to cause adverse health effects. This is based on both the IOM findings and studies including several hundred participants, which have measured and reported safety and adverse outcomes data and consistently shown no significant serious adverse effects without valid evidence to the contrary. In addition, the NHMRC (2014) nutrient reference values (NRV) for magnesium recommend up to 350 mg of magnesium from non-food sources for children over eight years and adults, including pregnant and lactating women.

It appears out of place and inconsistent for the TGA to take a significantly more conservative approach than that which is agreed across the NHMRC and respected international agencies which have largely harmonised on a level of 350mg, *even* when taking into consideration the possibility of multiple supplements causing minor amounts from other supplement sources, which is addressed later in this part.

There are a number of scientific studies in which significant instances of the osmotic effect of magnesium was not observed, even at doses well above NHMRC suggested recommendation of 350mg/day:

- A double-blind, controlled crossover three cohort design study conducted by Ashmead et al. (2016) on healthy adults, in which 300, 450, or 600mg/day of either magnesium bisglycinate, dimagnesium malate or magnesium was compared against placebo in each cohort study. The findings of this study demonstrated that doses of 450-600mg of magnesium malate and

bisglycinate resulted in improvements in faecal consistency, and each type of magnesium was well tolerated. Gastrointestinal symptoms, when noted, were mild with no significant differences across test products and placebo; flatulence was the most prevalent symptom during both placebo and active study product consumption.

- A Cochrane review on Magnesium supplementation in pregnancy conducted by Makrides et al. (2014) included a high-quality double-blind randomized, controlled clinical trial by Sibai et al. (1989) designed to investigate the effects of oral magnesium supplementation during pregnancy on maternal systolic and diastolic blood pressures and the incidence of preeclampsia as primary outcomes. 400 women participated in the trial and the 185 women in the magnesium group received six tablets of magnesium-aspartate hydrochloride per day. Each of these tablets contained 60.8mg of elemental magnesium (a total of 365mg/day). Fourteen subjects in the placebo group and 11 in the magnesium group discontinued intake of tablets before the beginning of the third trimester. The remaining subjects took approximately 90% of the possible number of tablets, which were continued until onset of labour. The major reasons for stopping the medications were gastrointestinal symptoms (nausea, vomiting, diarrhea) and difficulty in swallowing the tablets. However, the incidence of gastrointestinal symptoms was similar in both groups; 7% in the placebo vs. 6% in the magnesium group.
- A small study of the effect of oral magnesium supplementation in suppressing bone turnover in postmenopausal osteoporotic women, oral magnesium citrate at doses of 1,830mg/day, was supplemented by women for 30 days with loose stools reported in two participants (Aydın et al., 2009), and a double-blind randomized multi-centre study including 99 women conducted by Bullarbo et al. (2018) administered doses of 400mg magnesium citrate per day in addition to multivitamin tablets containing magnesium in 35% of participants (the doses of additional magnesium varied between 30 and 150 mg/day). The study recorded an 11% drop-out rate, mainly linked to unspecified side effects.
- A 2008 double blind, randomized, placebo-controlled study evaluated the prophylactic effects of 600mg/day oral magnesium citrate supplementation in patients with migraine without aura. Of the 30 patients allocated to the magnesium treatment group, four reported soft stools or diarrhoea and two gastric irritation, though none of the side effects caused discontinuation of the treatment (Köseoglu et al., 2008).
- Peikert et al. (1996) found that while minor and tolerable gastrointestinal effects were experienced by some participants taking 600mg magnesium citrate for 12 weeks, these effects required no further treatment and represented a reasonable adverse event profile.

- A study on magnesium therapy in coronary heart disease including 505 patients, receiving either 300mg or 600mg magnesium citrate per day (mean treatment 51 days) reported 1.8% of patients had experienced any gastrointestinal effects (Wilimzig & Vierling, 1991). Another study (Wilimzig & Pannewig, 1994) on high-dose oral magnesium therapy in pregnancy, included 366 women, administered either <300 mg, 300mg or >300 mg (up to 900mg) magnesium citrate per day. 96.2% of the women were treated with at least 300mg and the treatment was well tolerated, with only 3% of patients reporting mild diarrhoea.

On balance, these studies demonstrate that doses of magnesium ≥300mg/350mg per day are well tolerated among various populations, with adverse effects being largely comparable between treatment and placebo cohorts.

**Organic magnesium compounds and Magnesium chelates**

It is important to differentiate between the different magnesium salts, as certain types of magnesium salts are shown to be more absorbable and therefore, have higher bowel tolerance than others. This is already recognised in the in the current *Therapeutic Goods (Permissible Ingredients) Determination (No. 3) 2020* (the Determination), which specifies warnings only for magnesium hydroxide, magnesium sulfate, magnesium pyruvate and bittern, types of magnesium known to have higher osmotic laxative effects. It should be noted that dietary factors also play a role in the absorption of magnesium. For example, high levels of dietary fibre from fruits, vegetables, and grains can decrease magnesium absorption, and absorption can also be influenced by dietary protein (EVM, 2003).

The NHMRC quantity of 350mg/day is based on studies in which significant instances of the osmotic effect of magnesium was not observed, even at doses *well above* Australian UL of 350mg:

- Supported by the findings of Fine et al. (1991), Bashir et al. (1993) conducted a randomized, double-blind, crossover trial consisted of two 6-week treatment arms during which 21 participants received alternately enteric-coated magnesium chloride of 3,204mg/day in divided doses (equivalent to 15.8 mmol of elemental magnesium) and placebo. The study found that the intervention, caused troublesome gastrointestinal symptoms in 6 participants however, no serious adverse effects were reported.
- Marken et al. (1989) conducted a randomized, double-blind, placebo-controlled, crossover study to determine if supplemented magnesium oxide would produce changes in the lipid profile. Fifty normal volunteers received placebo or magnesium oxide, 400 mg capsules, twice a day (total 800mg, equivalent 476mg of elemental magnesium) for 60 days then switched to

the alternate treatment. Though the authors state that the cathartic dose of elemental magnesium is 1200-3000 mg, a 36% incidence of diarrhea was observed.

- Ricci et al. (1991) conducted a prospective randomized clinical trial on oral tocolysis with magnesium chloride. After a 12-hour contraction-free period on intravenous therapy, participants were administered either 535mg of magnesium chloride every four hours, another therapy or no therapy. The interventions continued until delivery or completion of 36 weeks' gestation. In this study, 80% of participants who took the magnesium intervention did not experience side effects.

While inorganic compounds are included in each of these studies, it is widely accepted that magnesium absorption varies between organic and inorganic compounds. Evidence provides that organic magnesium compounds generally have a higher bioavailability than inorganic compounds (Mühlabauer et al., 1991; Firoz & Graber, 2001; Kappeler et al., 2017) and malabsorption associated with poor inorganic magnesium absorption may create an osmotic gradient in the colon, resulting in loose stools or diarrhea (Weiss et al., 2018). In addition to those types currently specified in the Determination, preparations including magnesium carbonate, magnesium chloride and magnesium oxide have demonstrated this effect (Ranade, 2001; al-Ghamdi et al., 1994), while organic compounds and chelates, such as magnesium glycinate, threonate and malate, are more completely absorbed and more bioavailable, thereby minimising gastrointestinal discomfort (NIH, 2020; Weiss et al., 2018).

In addition to those studies on magnesium citrate outlined previously, a review of several studies by Rylander (2014) and a separate study by Lindberg et al. (1990) also found that organic magnesium salts, such as magnesium citrate, have a higher solubility and therefore absorbability than inorganic magnesium salts. Walker et al. (2003) also found magnesium citrate and amino acid chelate to show superior bioavailability compared with inorganic compounds. Furthermore, though organic compounds have higher solubility, only limited levels of elementary magnesium are provided in contrast to inorganic salts which provide higher loading of elementary magnesium (Blancquaert et al., 2019) thereby, provoking an osmotic effect.

The SCF (2006) provides that 360-365mg magnesium per day is stated as the lowest dose at which there was an observed adverse effect (LOAEL). The SCF data summary included twenty studies in the review; four of these studies used doses of ≤250mg/day, three of which included organic magnesium types. Of the remaining sixteen studies which included doses >350mg/day, ten instances of mild diarrhoea were reported in seven of the organic magnesium studies which included either pyrrolidone carboxylic acid salt, magnesium aspartate HCL or magnesium lactate citrate (excluding one study which used doses well out of the realm of any listed medicines on the ARTG of 1095 mg/day),

compared with 29 reports of diarrhoea in the eight inorganic magnesium studies, which included magnesium hydroxide, magnesium chloride, magnesium chloride oxide and magnesium oxide. This represents a **three-fold increase** in diarrhoea occurrence for inorganic magnesium compounds. Consequently, the evidence demonstrates that it is not appropriate to provide the same limits and same requirements to organic and inorganic magnesium compounds.

Of the studies reviewed for the organic compound, magnesium aspartate HCL, one double blind randomised crossover study of one month's treatment with magnesium aspartate hydrochloride 15 mmol daily given in the form of two tablets three times daily for one month, found this type of magnesium was well absorbed and all patients who entered the trial completed it without any adverse effects, and no patients complained of diarrhoea (Cappuccio et al., 1984). Another study of including 278 pregnant women, given 15 mmol of magnesium aspartate-hydrochloride; divided into six tablets to be taken daily, found the frequency of complaints attributed to the tablets [intervention and placebo] was low and comparable in the two groups. In the magnesium group one woman complained of diarrhoea, four of nausea, six of vomiting and six of heartburn; in the placebo group two complained of diarrhoea, one of nausea, 10 of vomiting, six of heartburn and one of fullness (Spätling & Spätling 1998). Four of the studies on magnesium aspartate HCL were only applicable to children. The included study on magnesium lactate citrate found oral administration of magnesium for 6 weeks satisfactorily bioavailable (Gullstead et al., 1991).

Magnesium gluconate has also shown to be better tolerated than inorganic magnesium salts as it appears to be better absorbed and causes less diarrhoea (al-Ghamdi et al., 1994), and magnesium diglycinate (chelate) appears to offer greater bioavailability and tolerability for patients with impairments in magnesium absorption and resulted in fewer bowel movements when compared with an inorganic magnesium salt (Schuette et al., 1993).

The conservative approach to encompass all magnesium salts in the proposed warning statement does not reflect the tolerability of and risk profile of organic compounds based on the available literature.

It stands to reason that magnesium types with a higher bowel tolerance, such as organic compounds and chelates should, therefore, be exempt from carrying the proposed warning statements. To avoid confusion, potential post-market compliance issues or differences in interpretation of the literature, the forms of magnesium which require this warning should be specified to include inorganic compounds, rather than encompassing all magnesium types that may be considered ‘easily dissociable magnesium salts’.

**Simultaneous magnesium-containing supplements and medications**

The Australian Bureau of Statistics Australian Health Survey: Usual Nutrient Intakes, 2011-12 (2015) reported that 41% of males aged 19 years and over and 35% of females of the same age group had inadequate intakes of magnesium. From this data, it may be reasonable to conclude that many Australians may be taking, and would benefit from, a magnesium supplement or a multivitamin containing magnesium. It is consequently necessary that any statement does not state 'this product' without adequate information for the consumer to discern which substance and at what level is causing the stated effect (in this case laxative or diarrhoea) so that they can make an informed choice and use it in an informed way. Otherwise, misconceptions can occur that weaken quality use of medicines rather than strengthen it, or the statement reduces the likelihood that the consumer may take a product that would be of nutritional benefit and in the case of magnesium, help with muscle performance and symptom relief amongst other important supportive benefits which are regularly reported by magnesium users.

The Australian Government Guide to Regulatory Impact Analysis and the TGA regulatory framework, Version 1.0, May 2012, recognises that regulatory systems aim to reduce risks but it is impossible to seek to avoid all risk, and that the TGA's risk management approach is about reducing the impact of risk to an acceptable level. In this instance, the conservative approach of 250mg proposed by the TGA when compared to the evidence and comparable agencies, appears to be trying to account for all risk rather than an acceptable level of risk. It is stated to be due to consumer ignorance relating to the effects from common self-selected listed medicines containing magnesium and due to the large number of magnesium-containing supplements and medications, which may be taken simultaneously. The TGA's consultation notice provides that advice was sought from the Advisory Committee on Complementary Medicines (ACCM) on the laxative effects of easily dissociable magnesium salts at the 24th ACCM meeting, which informed the TGA's proposed warning statement for medicines not indicated for laxative use containing 250 mg or more elemental magnesium per maximum recommended daily dose for children and adults greater than nine years of age. However, this pre-justified solution does not consider the extent of the available literature or the recommendations provided by comparative regulatory agencies and research organisations, or the nature of magnesium supplementation in Australian products.

It is acknowledged that the diarrhoea and laxative effects of inorganic magnesium salts are due to the osmotic activity of unabsorbed salts in the intestine and colon and the stimulation of gastric motility. However, these effects, if experienced at all, are mild in nature and completely reversible, and occur in only a small percentage of people. A search of the Database of Adverse Event

Notifications (DAEN) on 16 September 2020 for ADRs related to magnesium between 01/01/2010 – 16/06/2020 revealed 337 cases in total, with fewer than half (156) of these related to listed medicines. Given the TGA's concern primarily pertains to diarrhoea and laxative effects of magnesium salts, it should be noted that diarrhoea was reported for 33 listed medicines in this ten-year period with the largest number of gastrointestinal ADRs among these 156 medicines attributed to a medicine containing magnesium oxide (three medicines eliciting a total of ten ADRs where the tradename was not specified were also included in this number). Further, additional medications (many of which did not contain magnesium) were suspected in approximately nine cases of reported gastrointestinal ADRs. Considering that magnesium is a popular supplement for its health benefits with millions of units sold yearly, this is a very minimal ADR profile.

In drawing assumptions that consumers would accidentally take large amounts of magnesium from different sources, the TGA has not provided any analysis of the types of products available and the typical magnesium amounts, indicating that the level of risk is only being guessed at without analysis. Consideration of this is critical to understanding the risk profile and whether it is a high and prevalent risk or a low risk.

In our view it is very unlikely that there is a significant level of accidental co-administration of significant amounts of magnesium from different sources. Compared to vitamins and many other mineral supplements, it is difficult to include any large amount of magnesium (or calcium) in tablet or capsule presentation, including almost all multivitamin preparations. They generally contain small amounts of magnesium, most commonly around 10-50mg. Consumers seeking a magnesium supplement in particular specifically seek out a supplement that provides an appreciable amount of equivalent magnesium, generally 150mg or greater and very rarely over 300mg, depending on their need or purpose. These supplements are labelled specifically either as magnesium supplements (particularly tablets and capsules) or as powders (rarely, liquids) labelled as magnesium powders or muscle-easing powders with an appreciable amount of magnesium. In other words, consumers are not taking a high-dose magnesium supplement unless are aware of it (by taking it of their own volition or by practitioner recommendation to take higher-dose magnesium), and the intake of magnesium from supplements that are not specifically called-out as magnesium supplements is generally very low. Taking multiple high dose magnesium supplements is therefore highly unlikely – it would not make sense to take more than one muscle or magnesium powders when they are clearly marked for their main purpose of providing magnesium. Consumers/practitioners select a single high dose magnesium supplement, to do otherwise would be as illogical as taking multiple brands of paracetamol to obtain pain relief, or multiple brands of high dose calcium to obtain calcium, it simply

should not occur except on the rarest of occasions. Whilst it is possible to conceive it is not impossible, regulation and law cannot account for the very rarest and unusual risks to individuals – regulation and law is designed to account for the '*reasonable person'*.

The risk of taking additional magnesium from *other* supplements is likely only to occur through multivitamin/mineral supplementation, at the low levels of around 10-50mg. An increased risk of osmotic diarrhoea taking 250mg vs 280 or 290mg magnesium is extremely negligible considering the evidence available as outlined in this submission. Whilst in some other regulatory scenarios, multiple medications may post a pragmatically realistic issue, in the case of magnesium supplements, there appears to be an extremely low risk of consumers taking multiple high dose magnesium supplements that would justify lowering the upper suggested limit of 350/360mg agreed on by other Government agencies and regulators, and particularly not a level of risk that justifies an conservative approach of 250mg. The application of the proposed requirements to 250mg is in this situation clearly a regulatory overreach. The TGA approach should be aligned with other agencies and Government recommendations at 350mg.

**Recommendation – Easily Dissociable Magnesium Salts**

1. CMA propose an alteration of the proposed laxative warning statement for **inorganic** magnesium compounds for individuals aged nine years or older to **>350mg** (along with re-examination of amounts to the other age groups), to align with the Australian Government's NHMRC recommendation and those of other international regulators and research organisations.
2. The statement should not apply to magnesium types with higher tolerability, including organic compounds and chelates, as per the research outlined; and
3. The omission of the warning statement 'Not suitable for infants under the age of twelve months' (or words to that effect)', in keeping with the current requirements which do not require the additional statement. It is also extremely unlikely that a listed medicine magnesium supplement would be recommended for or given to an infant other than part of an infant formula (food) therefore, this statement is unnecessary and is regulatory overreach considering that there is already highly limited label space on listed medicines. This requirement has no dose limitation and would need to be applied to ***many thousands*** of magnesium products creating extremely high red tape relabelling requirements for a situation that is extremely low risk or likely to occur. Any parent is <u>not</u> going to give an infant a muscle relief powder clearly intended for adults in sports or similar, nor a women's or men's multivitamin or any other product in a divided dose form/tablet or capsule format, or any

number of other magnesium supplements on the market clearly marketed to adults for adult indications. This would clearly by unnecessary and absurd regulation. If the TGA is aware of or concerned about a specific risk to age group of infants, then instead of the warning statement it would be acceptable to have a requirement that sponsors do not include a dose recommendation for infants under the age of 12 months in the directions for use, and almost all magnesium supplements - if not all, are already in compliance with this requirement.

4. The warning statement should inform quality use of medicines for consumers, and be as short as possible for both label space considerations and to ensure that consumers read the statement, as it is known that lengthier statements are less likely to be read and understood. The statement 'this product' is non-specific and has the likelihood to worsen misunderstandings rather than improve quality use of medicines. Further, the osmotic laxative effect is no greater or worse than the very commonly available medicines with sugar alcohols, which are required to include a different but appropriate statement 'Products containing (name of sugar alcohol) may have a laxative effect or cause diarrhoea'. To avoid consumer confusion and a myriad of different requirements for substances with the same effect, such statements should also be aligned for best practice regulation, therefore it is proposed that the statement should be amended to account for both of the above:

   'High dose magnesium may have a laxative effect or cause diarrhoea'.

Proposed amendments to the consultation proposal are highlighted:

Magnesium is a mandatory component of this ingredient.

When used in medicines:

a. with an oral route of administration;
b. not indicated for laxative (or related) use;
c. that contain inorganic magnesium salts; and
d. the maximum recommended daily dose for:
   i. children aged between 1 and 3 years (inclusive) provides 65 mg or more total magnesium;
   ii. children aged between 4 and 8 years (inclusive) provides 110 mg or more total magnesium; or
   iii. individuals aged 9 years or older provides 350 mg or more total magnesium;

the following warning statements are required on the label:

- 'High dose magnesium may have a laxative effect or cause diarrhoea (or words to that effect)'.

## Andrographis paniculata

Following a safety advisory issued by the TGA in May 2020 for *Andrographis paniculata* (Andrographis) due to adverse event reports which have associated the use of Andrographis with potential taste disturbances, the following warning statement has been proposed as a mandatory requirement:

- (ANDROT) Andrographis may cause taste disturbance including loss of taste. If you develop any adverse symptoms, stop use and seek medical advice (or words to that effect).

Andrographis' bitter taste is attributed to an active constituent andrographolide, which is a diterpenoid lactone found in the plant (Okhuarobo et al., 2014), the extent to which the bitter taste is experienced depends on individual physical and psychological differences, including the number of taste buds and personal preference (Zhang et al., 2018). A metallic taste (Hossain et al., 2014) and loss of appetite (Rajasekaran et al., 2016) have been observed in larger doses of Andrographis.

CMA notes that no international reports, other than those from Australia, could be located for *Andrographis paniculata* and taste loss/taste disturbance in The Uppsala Monitoring Centre's adverse reaction reporting database VigiLyze.

CMA also notes that, while the TGA found that COVID-19 was not considered to be a confounding feature of the reports of taste disturbance, loss of taste may also be a symptom of COVID-19 and Andrographis is commonly used in immune support, cold/flu prevention. As such, health professionals and consumers alike awareness of the possible development of taste disturbances in conjunction with the use of products containing Andrographis has been facilitated through the May 2020 TGA safety advisory.

The TGA consultation reports receiving 226 reports of ageusia (loss of taste), dysgeusia (taste distortion), hypogeusia (decreased sense of taste) and/or taste disorder related to products containing *Andrographis paniculata* by 30 July 2020. The majority (91%) of the cases were associated with a single product, with only 9% of cases associated with a total of nine different products which also contain Andrographis. This 9% (twenty) reports of taste loss/taste disturbance are, nonetheless, considered by the TGA to be significant signal requiring investigation.

On 14 September 2020, a search of the DAEN for 'Andrographis' between 01/01/1971 - 14/06/2020 (the latest searchable date at the time) yielded a result of 48 medicines. Of these, nine medicines were associated with Hypoaesthesia, oral; Taste disorder; Paraesthesia oral; Ageusia; or Dysgeusia. Two of these medicines no longer appear to be listed on the ARTG. Nine medicines identified in a period of nearly 50 years in association with the above terms does not reasonably warrant a blanket statement for all Andrographis containing products.

Prior to applying a blanket warning statement to all Andrographis containing products, further understanding is needed in relation to the particular characteristics of the products associated with the ADRs to determine any specific commonalities. Particularly, whether the type of extraction solvent used in these formulations is relevant, or if there are other relevant factors. Considering that 91% of reports relate to a single product which has already been updated accordingly, there is not enough additional local or international data to understand the cause or to apply this to all other Andrographis products at this time.

As an example, the solubility of andrographolide(s), the constituent attributed to Andrographis' bitter taste, differs between aqueous solvents and methanolic/ethanolic solvents (Mussard et al., 2019). Water-based extracts are likely to have fewer, if any, associated reports of taste disturbance when compared with certain ethanolic/methanolic extracts however, there is not enough data currently available to draw any definitive conclusions that are significant enough to apply the statement to largely unaffected products.

We agree that caution should be applied, including an approach of ongoing monitoring and the continuation of existing pharmacovigilance to gain more relevant data establish any significant correlations, such that this issue can be monitored and revisited when appropriate amounts of data may be available. If a better and clearer trend is established between certain types of extract and ADRs, then further action for other Andrographis products (some or all types) may be warranted. Based on the information available, and that the TGA website already raises awareness for practitioners in particular, we believe it is necessary that monitoring continues over the next 12 months or more to ensure any actions are in fact warranted and correctly applied to relevant products only, and that this proposal is revisited at a later date once more reliable data to both justify a decision and inform the nature of that decision is available. We note that an incidence of 20 reports amongst the millions of Andrographis doses taken yearly, other than the affected product which is already amended, is an extremely low incidence, and there are many thousands of ADR reports for other OTC and non-prescription medicines with an ADR incidence of this amount of greater, even for more serious reactions, that do not require warning statements, therefore, this proposal remains out of place for TGA best regulatory practice other than the action already taken for the prime causal product.

**Recommendation**

1. With insufficient information and data to justify the proposed statement currently, we propose that it is suitable to continue TGA and industry monitoring for 12 months or more to gather data with a view to revisiting any proposal as required.

## Propolis containing ingredients (additional item)

The current requirements in the Permissible Ingredients Determination No.3 2020 (the Determination) for propolis, propolis balsam, propolis dry extract, propolis liquid extract, propolis resin and propolis tincture provide that:

> "Lead is a mandatory component of Propolis.
>
> The concentration of lead in the medicine must be no more than 0.001%.
>
> When used topically, the medicine requires the following warning statement on the medicine label:
>
> -(PROP1) 'WARNING: Propolis may cause skin irritation. Test before use'
>
> When used for other than for topical, the medicine requires the following warning statement on the medicine label:
>
> - (PROP2) 'Warning: Propolis may cause allergic reactions. If irritation or swelling of the mouth or throat occurs, discontinue use.'"

The limit was implemented many years ago, before there were mandatory elemental impurity requirements and when lead in propolis was an issue due to lead paint used in beehives (which is no longer used). Elemental impurities limits on raw materials and finished products include the USP232 for raw materials, the USP2232 and the ICHQ3D for all other dosage forms. The TGO101 for capsules and tablets also relevantly captures the above. This makes the additional requirements in the Determination a redundant and duplicative legislative requirement for elemental impurities (in this case, lead).

Historically, but not currently, the use of lead-based paints in hives was common. A review of the published literature on heavy metal contamination of pollen, beeswax and propolis found that the main contamination danger of lead in propolis is thought to originate from apicultural practices, such as lead based paints and collection methods, rather than from environmental influences (Bogdanov, 2006; Sales et al., 2006). There are very few lead-based painted hives left in use in contemporary apicultural practice and there has been a significant reduction in levels of lead in propolis in the last decade. In addition, as of May 2020, a number of WHO member states have committed to legally binding controls on lead paint in general, including China, India, New Zealand and Australia (WHO, 2020).

**Recommendation:**

1. Removal of the duplicative requirement for lead which was historically required but is no longer required due to developments in other TGA regulatory requirements [default standards] in addition to the removal of the environmental cause due to modernised apicultural practices.

## Caffeine

Caffeine has not been included in the consultation. For the reasons outlined below, we believe that it is critical that the TGA's Complementary Medicines and OTC Branch commit to an appropriate consultation of caffeine well before the March 2021 deadline with un-consulted changes that are now in direct disparity with numerous relevant aspects of safety reviews and proposals made by FSANZ and also by the TGA's Scheduling Committee. If appropriate changes can not be made rapidly in consultation with FSANZ, then the March 2021 guideline must be extended to March 2022 as the first step until the TGA consultation and TGA-FSANZ interorganisational considerations of harmonising extremely similar products are completed and appropriately harmonised. This is with the exception of a 1% w/v limit of caffeine in liquid listed medicines, which could continue to be implemented by March 2021 as a safety precaution.

CMA's approach to safe and balanced regulation of caffeine products has been consistent throughout the years, in seeking safe but appropriate use and regulation of caffeine. In May 2018, CMA advocated to the TGA that adequate advisory statements on therapeutic goods should raise awareness of caffeine levels so that consumers were aware of the level of their caffeine consumption on packaged products, coupled with appropriate quantity restrictions (up to 600mg per day). This was well before the coroner's report in June 2019 of an accidental overdose from a concentrated product of unknown origin.

CMA continues to seek a safe, appropriate, and timely approach to caffeine.

Though not explicitly included in the Permissible Ingredients annual changes 2020-21 consultation, we are strongly of the view that if the TGA is to adequately perform best practice regulation by appropriate community consultation, that this substance should have consulted in this round of consultation.

By comparison, the TGA's 'sister' agency the food regulatory FSANZ has conducted three consultations to date on caffeine to date, with more in the pipeline. The most recent consultation was a consultation about the next phase of consultation, examining the same technical and policy issues relating to caffeine as those which are relevant to listed medicines, whilst the Complementary Medicines and OTC Branch has not done any consultation at all, including a lack of consultation on those issues which were not urgent and on issues that were not previously consulted by either the COMB in 2017-18, or by the ACCS/ACMS and Scheduling Delegate as part of the Scheduling process in 2019-20.

CMA fully supported the Scheduling decision of 5% caffeine, however there are *other* decisions for caffeine included in the Permissible Ingredients Determination that are not warranted and not supported and not consulted. There are therefore, a number of caffeine decisions that could have and should have been subject to further consultation for the Government to conform to its regulatory practice expectations to publicly consult with the community on decisions that affect them.

The recent FSANZ proposal paper P1054 – Pure and highly concentrated caffeine products, puts forth the view that the TGA and FSANZ are aligned in respect of a 5% limit for undivided preparations (U/P), this is in fact not the case; the main category of therapeutic goods which contain caffeine are listed medicines, which are currently not permitted to include 5% caffeine in U/P, they must include 4%, or from March 2021, only 1% - despite this not being subject to formal assessment or consultation, and despite similar consultations by FSANZ.

Therefore, foods and therapeutic goods are not primarily aligned at a 5% permissive limit. Caffeine as a substance does not discriminate between regulatory boundaries however, collaboration does not appear to have occurred, evident by a siloed approach continuing between the organisations, a disjointed approach to community consultation between organisations and the wide gap between formulation and labelling policy approaches for relatively similar goods.

There is currently a "two-pronged" approach to caffeine in foods and listed medicines and while there are some similarities, there is no acknowledgement that the two pronged approach results in different and illogical approaches and confusing information for industry and consumers on a number of products which, from a consumer's view, may be virtually indistinguishable. This will undoubtedly lead to consumer confusion, possible compliance issues, and other unexpected and discordant outcomes. This two-pronged approach is not appropriate to caffeine and is clearly inconsistent in a number of respects where it should be consistent.

Whilst registered (including complementary) medicines are permitted to contain 5% in U/P (but not listed medicines), this is counterproductive to the Australian Government attempting to increase safety of caffeine products. Consultation is important such that the decision maker should be taking into consideration all information from the community before making a decision, not making decisions based on opinion or limited information. The responsibility of a decision maker is not only the direct effect of regulation, but also the indirect effect of regulation. The inappropriate removal of safe levels of caffeine from listed medicines at levels lower than that which is allowed in foods therefore pushes manufacturers not from the listed medicine pathway to the registered medicine pathway – which is largely resource and cost prohibitive for powders/liquids containing caffeine –

but instead to use the food regulatory pathway to supply caffeine goods. The food regulatory pathway has far fewer manufacturing controls and oversight and far less opportunity for post market monitoring than PIC/S GMP listed medicines on the ARTG. The misalignment of these two categories therefore significantly increases risk to the consumer, and further, most concerningly, highly increases their risk of purchasing much more poorly controlled and manufactured (more highly concentrated) caffeine products from international e-commerce websites (which often appear to be Australian websites or no different to purchasing from Australian websites). These indirect effects of regulation are in direct contrast to the Government's goals to improve caffeine regulation and safety. It is very difficult in this context, considering the recent dangers that have been highlighted of buying unregulated products, to understand the TGA's reluctance to conduct appropriate consultation with the community on caffeine in listed medicines.

Despite extended safety reviews which found the 5% limit to be appropriate, an inherent disparity still exists between the current 1% limit in undivided preparations included in the Determination and the 5% limit set for food by both FSANZ and the Scheduling framework recommendation.

Our submission to FSANZ - P1054 (Nov 2019) also noted that the proposal does not sufficiently mitigate accessibility through import pathways for personal use, and that there are potential risks of Australian overregulation through excessive restriction of in-demand products from consumers may cause some to revert to personal importations of either legal but significantly more concentrated or illegal substances. Therefore, regulatory restrictions must be balanced with consumer demand in order to have the most positive net impact.

This TGA imposed, unconsulted limit of 1% applicable to all undivided preparations from March 2021, negates the fact that listed medicines are produced in manufacturing facilities which are required by law to conform with pharmaceutical-level GMP requirements under the international Pharmaceutical Inspection Co-operation Scheme (PIC/S), with regular Product Quality Reviews, in comparison with foods which have less strict manufacturing controls, but are permitted to have up to 5% caffeine.

The Australian Public Service Commission's introduction to the concept of the Whole-of-Government raises issues relevant to the caffeine issue:

> *A vital issue for the APS in delivering quality advice, programs and services is ensuring work is effective across organisational boundaries. Making whole of government approaches work better for ministers and government is now a key priority for the APS. There is a need to achieve more effective policy coordination and more timely and effective implementation of*

*government policy decisions, in line with the statutory requirement for the APS to be responsive to the elected government. Ministers and government expect the APS to work across organisational boundaries to develop well informed, comprehensive policy advice and implement government policies in an integrated way.*

*In addition, the Australian public increasingly expects services to individuals, business and communities to be tailored to their particular needs. They expect government to take full advantage of technology to do business better. There is now more expert and informed scrutiny of government, making the public more quickly aware of any approaches that appear to conflict.*

Of all policy issues that stand out as being clearly appropriate for a Whole-of-Government approach, there is none so less than caffeine, a substance in high demand and ubiquitously available in naturally occurring foods as well as formulated, packaged preparations for supplementary use in both foods and therapeutic goods.

Caffeine does not discriminate and consumers rarely if ever distinguish between these regulatory siloes. Why then does the Government's regulatory schemes continue to regulate differently, consult separately, and reach different conclusions for caffeinated products that are in the main, conceptually and functionally indistinguishable for consumers?

Collaboration between FSANZ, the TGA and peak industry bodies is necessary to arrive at a consistent approach immediately and into the future, as this enables consistency and clarity for stakeholders and equal application between Listed medicines and food products, providing a much clearer, more sensible, and easy to navigate regulatory landscape for both consumers and businesses.

The final regulatory outcomes between the approach to foods and listed medicines should not be significantly different unless there are specific supportable, well-examined, consulted-upon reasons to justify a difference for each class of sub-category of goods.

For foods and listed medicines that are not the subject of a Schedule in the Poisons Standard, and that are not the subject of different specific requirements for the purposes of a specific Food Standard, we support that at a minimum, packaged foods and listed medicines are treated in the same manner on the following items:

| **CMA *preliminary* position on caffeine (pending further FSANZ and TGA consultation on more specific details) – October 2020** |
|---|
| **Transition date for additional caffeine restrictions**<br><br>Initially set at March 2021, ongoing safety reviews and consultations demonstrate that the proposals are not aligned or appropriate and must be subject to further consultation, therefore, this date must be extended to March 2022. This is with the exception of 1%w/v on liquids as included in the row below, nonetheless, such a restriction will still require a change of wording to the existing requirement in the Permissible Ingredients Determination. |
| **Quantity restrictions on liquids** (*Liquid caffeine concentrate products* – foods and listed medicines)<br><br>**1% w/v** (equivalent to 100mg/10mL)<br><br>1% w/v is a more appropriate specification than '1%' for undivided preparations. However, it supports the current TGA general position on 1% for undivided preparations – provided it is only for liquids. Appropriate calculations of 1%w/v for liquids are detailed by the FSANZ proposal. Further, this aligns with the current proposal by FSANZ. 1%w/v is supported provided there is harmonisation between foods and listed medicines. Harmonisation protects industry and protects consumers, as noted above in our submission. |
| **Quantity restrictions on powders/solids in listed medicines and foods:**<br><br>**5% w/w**<br><br>**Appropriate and supported provided there is harmonisation between foods and listed medicines.**<br><br>This would be an increase from 4%/1% currently specified to 5%, which is appropriate considering the safety reviews that were conducted by both FSANZ and the TGA Scheduling section AFTER the Complementary Medicines and OTC Branch made the change to 4%/1% (without analysis or consultation). The FSANZ proposal provides that: Ingestion of a single serving of a heaped tablespoon of a caffeine powder containing 5% caffeine would be likely to deliver approximately 825 mg caffeine. Acute doses in this range would be unlikely to cause severe health effects in healthy adults, although they could be expected to be associated with unpleasant effects such as anxiety.<br><br>As noted earlier in our submission, alignment in this space protects consumers more than restricting caffeine in this space, by preventing consumer use of less regulated food products, and far less |

regulated products being easily obtained from e-commerce sites that are not subject to Australian regulations but which often appear to be Australian.

Note: Listed medicines containing >80mg per recommended daily dose are required to include:

- (CAFFLMT) 'Limit the use of caffeine-containing products (including tea and coffee) when taking this product.'

**Individually packaged portion-controlled caffeine products**

In the context of sports supplements for adults, a higher quantity of caffeine is permitted in foods (for example, 160mg per dose instead of 100mg per dose). This higher quantity per individual dose must be harmonised for sports supplements that could be either foods or listed medicines. Therefore, listed medicines that are sports supplements must be permitted to harmonise to food sports supplements at 160mg per portion controlled dose for adults.

This is critically relevant to consider in respect of the Sports Supplements consultation which has declared that some products which are currently regulated as foods will be required to be therapeutic goods.

**Caffeine analogues**

This must be considered in respect of the Sports Supplements consultation to ensure there is clarity for industry without causing costly errors or major competitive misalignment for Australian businesses trying to compete for Australian consumers' attention within an international e-commerce landscape.

**Sensitive subpopulations – Children**

The final consultation outcomes between foods and listed medicines must be consulted together and harmonised unless there is a specific and justifiable reason to take a different approach for a specific sub-category.

Currently, listed medicines require an 'Adults only' statement (or words to that effect) if there is >10mg caffeine per recommended daily dose.

**Sensitive subpopulations – Pregnant women**

The final consultation outcomes between foods and listed medicines must be consulted together and harmonised unless there is a specific and justifiable reason to take a different approach for a specific sub-category.

Currently, listed medicines with more than 10mg of caffeine per recommended daily dose require:

- (CAFFPREG) 'Caffeine intake more than 200 mg per day is not recommended during pregnancy or breastfeeding.'

For sensitive populations, we note that public health information is more likely to be a successful approach than additional warning statements on formulated products, considering that the majority source of caffeine from pregnant women and children is dietary tea, coffee, and chocolate. Therefore label warnings on a limited number of consumer goods that contain caffeine should not be considered a substitute for a wider and more effective Government approach, and that any crucially necessary warning statements on products should be kept short and effective which has a greater effects on consumers and more achievable for industry.

**CYP1A2**

Caffeine does not discriminate between sources. The Government must be consistent about their purpose and intent when messaging in regard to caffeine.

The CAFFCYP warning was added to listed medicines containing more than 80mg caffeine, without consultation and without specific justification being provided to the public on its relevance, need, context and usefulness. Medical practitioners do not regularly test for CYP1A2 or apply its meaning in context of caffeine. There are no Government webpages advising consumers on how to approach caffeine in respect of CYP1A2. There do not appear to be any Department of Health medical or consumer guidelines or information, or any guidance for medical practitioners by the RACGP in respect of CYP1A2.

A single nucleotide polymorphism has been identified as the major source of inducibility of CYP1A2. How caffeine is metabolised further depends on which allele is present. In addition, there are vast numbers of substances, and environmental factors, that interact with CYP1A2 including tobacco, oral contraceptives and various other medicines; foods such as cruciferous vegetables and curcumin; and even heavy exercise. Therefore, a combination of multiple factors could lead to a greatly increased or reduced activity of CYP1A2, regardless of caffeine consumption (Southward et al., 2018).

CYP1A2 and other metabolic enzymes are affected by a wide variety of foods and medications that do not include a warning statement in relation to CYP1A2 and only in very rare or extreme circumstances for other metabolic enzymes. This warning statement sits completely alone and contrary to normal regulatory practice, with capacity to cause confusion as to why it is present on some substances but not others, and on some caffeine products but not others, and with absolutely no supporting relevant health information or Government guidelines or practitioner guidelines. It has not been subject to

analysis as to its appropriateness or relevance, usefulness or function, and should not have been introduced as a knee-jerk reaction without any public consultation.

There are not serious reports of caffeine interaction with CYP1A2 or other drugs, the warning statement is unjustified and out of context for meaningful understanding and application to the community for caffeine and unless an environment develops that clearly supports the relevance and application of such a statement it remains out of place and as such we firmly oppose its requirement on both foods and listed medicines:

Not supported for either foods or listed medicines:

- (CAFFCYP) 'Caffeine interacts with enzyme CYP1A2 in the liver. Consult your health professional before taking with other medicines' (or words to that effect).

**Caffeine present in non-proprietary and proprietary flavouring substances**

Any regulations devised must take into consideration that small amounts of caffeine may be present in proprietary flavouring ingredients. The exact information and quantities present in flavouring ingredients may not be available to manufacturers of listed medicines and foods. Any regulations should take this into consideration and not apply requirements to small amounts of caffeine content (such as up to 10mg) as part of flavouring compounds.

**Imported products**

In regard to products imported for personal use, we note that there are e-commerce websites that present as if they are or may be Australian websites and promise rapid delivery, and as such, there appears to be a lack of awareness of consumers that they may be purchasing international products or that they have reduced safety protections. In a world where consumer good purchases increasingly occur in an online e-commerce environment, the Government must consider appropriate measures for consumers and to ensure a balanced approach and relatively fair playing field for local Australian manufacturing, as suggested by the Section 18(2) considerations.

## Recommendations for caffeine summary:

1. Consultation on caffeine in listed medicines, in alignment with FSANZ.
2. Align listed medicine restrictions with the FSANZ consultation to protect both industry and consumers:
    - 1% w/v for liquids

- 5% for powders, solids
- Harmonised sports supplements requirements across both categories (for example, 160mg per dose on individually packaged portion controlled doses as sports supplements in adults)
- Harmonised, sensible and strategic approaches to other matters including sensitive subpopulations, analogues, flavourings, and other issues.
- Remove CAFFCYP

## Conclusion

While the consideration of risk is important to any good decision-making process, the ongoing escalation of perceived risks relating to Listed medicines which are already considered low risk cannot be arbitrarily used as the sole basis for non-empirical, anticipatory decisions which is contrary to Australian Government regulatory principles outlined in guidance for regulators. Any proposed regulatory measures should necessarily consider reasonable strategies which enable consumer safety, only regulation where it is necessary and of value – particularly warning statements as consumers begin to ignore lengthy statements that are of decreasing relevance. They must be also be balanced with consumer demand and any potential costs to industry associated with the proposed measures to reduce or eliminate the perceived risks. The measures proposed by the TGA in relation to the Permissible ingredients annual changes 2020-21 present both an over estimation of the potential benefits of the proposed measures with a lack of complete regulatory analysis compared to comparable scientific organisations such as FSANZ, and an under-estimation of potential costs to consumers; by impacting their ability to self-select appropriately labelled products; and to the complementary medicine industry; by increasing unnecessary regulatory burden.

The strict regulatory requirements around low risk listed medicines in Australia and complementary medicine sponsor's commitment to providing efficacious products of a high standard and quality, contributes to a safe environment for consumers to self-select complementary medicines.

Continued access to affordable supplements which are supported by a low risk safety profile, and that display only clear, necessary and appropriate information, affords consumers the ability to make informed choices and to achieve and maintain optimal health, while supporting Australian manufacturing and export and further reducing the economic burden on Australia's health care sector.

# References

**Easily dissociable magnesium salts**


al-Ghamdi, S. M., Cameron, E. C. & Sutton, R. A. (1994). Magnesium deficiency: pathophysiologic and clinical overview. *Am J Kidney Dis*. 24(5),737–752. doi: 10.1016/s0272-6386(12)80667-6

Ashmead et al. (2016). A Randomized, Double-Blind, Three Cohort Crossover Study Assessing Gastrointestinal Tolerability of Magnesium Sources in Healthy Adults. *The Toxicologist, Supplement to Toxicological Sciences*, 150 (1), Abstract 2457. Available from: https://www.toxicology.org/pubs/docs/Tox/2016Tox.pdf

Australian Bureau of Statistics (2015). Australian Health Survey: Usual Nutrient Intakes, 2011-12. https://www.abs.gov.au/

Aydın, H., Deyneli, O., Yavuz, D. et al. (2010). Short-Term Oral Magnesium Supplementation Suppresses Bone Turnover in Postmenopausal Osteoporotic Women. *Biol Trace Elem Res.* (133), 136–143 (2010). doi: 10.1007/s12011-009-8416-8

Bashir, Y., Sneddon, J. F., Staunton, H. A., Haywood, G. A., Simpson, I. A., McKenna, W. J. & Camm, A. J. (1993). Effects of long-term oral magnesium chloride replacement in congestive heart failure secondary to coronary artery disease. *Am J Cardiol* (72), 1156-1162. doi:10.1016/0002-9149(93)90986-m

Blancquaert, L., Vervaet, C., & Derave, W. (2019). Predicting and Testing Bioavailability of Magnesium Supplements. *Nutrients*, 11(7), 1663. doi: 10.3390/nu11071663

Bullarbo, M., Mattson, H., Broman, A. K., Ödman, N. & Nielsen, T. F. (2018). Magnesium Supplementation and Blood Pressure in Pregnancy: A Double-Blind Randomized Multicenter Study. *J Pregnancy*. (29). doi: 10.1155/2018/4843159

Cappuccio, F. P., Markandu, N. D., Beynon, G. W., Shore, A. C., Sampson, B., MacGregor, G. A. (1985). Lack of effect of oral magnesium on high blood pressure: a double blind study. *Br Med J (Clin Res Ed)* 291(6490), 235-8. doi: 10.1136/bmj.291.6490.235

Expert Group on Vitamins and Minerals (EVM) (2003). Safe Upper Levels for Vitamins and Minerals. Food Standards Agency May 2003. Available from: https://cot.food.gov.uk/sites/default/files/vitmin2003.pdf

Fine, K. D., Santa Ana, C. A. & Fordtran, J. S. (1991). Diagnosis of magnesium-induced diarrhea. *N Engl J Med* (324), 1012-1017. doi:10.1056/NEJM199104113241502

Firoz, M. & Graber, M. (2001). Bioavailability of US commercial magnesium preparations. *Magnes Res*. 14(4), 257-262.

Gullestad, L., Dolva, L. O., Birkeland, K., Falch, D., Fagertun, H. & Kjekshus, J. (1991). Oral versus intravenous magnesium supplementation in patients with magnesium deficiency. *Magnes Trace Elem* 10: 11-16.

Institute of Medicine (1997). Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, DC: The National Academies Press. doi: 10.17226/5776.

Kappeler, D., Heimbeck, I., Herpich, C. et al. (2017). Higher bioavailability of magnesium citrate as compared to magnesium oxide shown by evaluation of urinary excretion and serum levels after single-dose administration in a randomized cross-over study. *BMC Nutr*, 3(7). doi:10.1186/s40795-016-0121-3

Köseoglu, E., Talaslioglu, A., Gönül, A. S. & Kula, M. (2008). The effects of magnesium prophylaxis in migraine without aura. *Magnes Res*. 21(2), 101-8. https://www.jle.com/en/revues/mrh/revue.phtml

Lindberg, J.S., Zobitz, M.M., Poindexter, J. R. & Pak, C.Y. (1990). Magnesium bioavailability from magnesium citrate and magnesium oxide. *J Am Coll Nutr*. 9(1), 48-55. doi:10.1080/07315724.1990.10720349

Makrides, M., Crosby, D. D., Shepherd, E. & Crowther, C. A. (2014). Magnesium supplementation in pregnancy. Cochrane Database of Systematic Reviews, Issue 4. Art. No.: CD000937. DOI: 10.1002/14651858.CD000937.pub2.

Marken, P. A., Weart, C. W., Carson, D. S., Gums, J. G. & Lopes-Virella, M. F. (1989). Effects of magnesium oxide on the lipid profile of healthy volunteers. *Atherosclerosis* (77), 37-42. doi: 10.1016/0021-9150(89)90007-5

Mühlbauer, B., Schwenk, M., Coram, W. M., Antonin, K. H., Etienne, P., Biek, P. R. & Douglas, F. L. (1991). Magnesium-L-aspartate-HCl and magnesium-oxide: bioavailability in healthy volunteers. *Eur J Clin Pharmacol*. 40(4), 437-438. doi:10.1007/BF00265863

National Health and Medical Research Council (2006). Nutrient Reference Values for Australia and New Zealand. Australian Government Department of Health and Ageing, New Zealand Ministry of Health. Canberra: National Health and Medical Research Council; 2006.

National Institutes for Health (2020). Magnesium Fact Sheet for Health Professionals [Fact Sheet]. Updated September 25, 2020. Available from: https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/

Peikert, A., Wilimzig, C. & Köhne-Volland, R. (1996). Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia*, 16(4), 257-63. doi: 10.1046/j.1468-2982.1996.1604257.x

Ranade, V. V. & Somberg, J. C. (2001). Bioavailability and pharmacokinetics of magnesium after administration of magnesium salts to humans. *Am J Ther*, 8(5), 345-57. doi: 10.1097/00045391-200109000-00008

Ricci, J.M., Hariharan, S., Helfgott, A., Reed, K. & O'Sullivan, M. J. (1991). Oral tocolysis with magnesium chloride: A randomized controlled prospective clinical trial. *Am J Obstet Gynecol*, 65(3),603-10. doi: 10.1016/0002-9378(91)90293-z

Rylander, R. (2014). Bioavailability of Magnesium Salts–A Review. *J Pharm Nutr Sci*. (4),57–9.

Schuette, S. A. , Lashner, B. A. & Janghorbani, M. (1994). Bioavailability of magnesium diglycinate vs magnesium oxide in patients with ileal resection. *JPEN J Parenter Enteral Nutr*. 18(5),430-435. doi:10.1177/0148607194018005430

Sibai, B. M., Villar, M. A., Bary, E. (1989). Magnesium supplementation during pregnancy: a double-blind randomized controlled clinical trial. *American Journal of Obstetrics and Gynaecology*, 161(1), 115-9. Doi: 10.1016/0002-9378(89)90246-9

Spätling, l. & Spätling, G. (1988), Magnesium supplementation in pregnancy. A double-blind study. *BJOG*, 95, 120-125. doi:10.1111/j.1471-0528.1988.tb06839.x

The Australian Government: Department of the Prime Minister and Cabinet (2020). Australian Government Guide to Regulatory Impact Analysis. Available from: https://www.pmc.gov.au/

VKM (2016). Risk assessment of magnesium in food supplements. Scientific opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy, VKM Report 2016:15 available from: https://vkm.no/english/riskassessments/allpublications/riskassessmentofmagnesiuminfoodsupplements.4.2375207615dac0245aee5130.html

Walker, A.F., Marakis, G., Christie, S. & Byng, M. (2003). Mg citrate found more bioavailable than other Mg preparations in a randomised, double-blind study. *Magnes Res*, 16(3), 183-191. https://www.jle.com/en/revues/mrh/revue.phtml

Weiss, D., Brunk, D. K. & Goodman, D. A. (2018) Scottsdale Magnesium Study: Absorption, Cellular Uptake, and Clinical Effectiveness of a Timed-Release Magnesium Supplement in a Standard Adult Clinical Population, *Journal of the American College of Nutrition*, 37(4), 316-327, doi: 10.1080/07315724.2017.1398686

Wilimzig, C. & Vierling, W. (1991). High-dosed oral magnesium therapy in CHD. *Zeitschrift für praktische Kardio Angiologie.* (12)91.

Wilimzig, C. & Pannewig, K. (1994). High-dose oral magnesium therapy in pregnancy. *Der Allgemeinarz.* 18/10994

## Andrographis

Hossain, S. et al. (2014). Andrographis paniculata (Burm. f.) Wall. ex Nees: A Review of Ethnobotany, Phytochemistry, and Pharmacology. *The Scientific World Journal*, vol. 2014. doi: doi.org/10.1155/2014/274905

Mussard, E., Cesaro, A., Lespessailles, E., Legrain, B., Berteina-Raboin, S. & Toumi. H. (2019). Andrographolide, a Natural Antioxidant: An Update. *Antioxidants (Basel)*, 8(12), 571. doi: 10.3390/antiox8120571

Okhuarobo, A. et al. (2014). Harnessing the medicinal properties of Andrographis paniculata for diseases and beyond: a review of its phytochemistry and pharmacology. *Asian Pacific Journal of Tropical Disease*. 4(3), 213-222. doi: 10.1016/s2222-1808(14)60509-0

Rajasekaran, A., Arivukkarasu, R. & Mathew, L. (2016). A systematic comprehensive review on therapeutic potential of Andrographis paniculata (Burm. f.) Wall. ex Nees. *Journal of Pharmacognosy and Phytochemistry*, 5(5), 189-199.

Zhang, X. et al. (2018). Determination of Bitterness of Andrographis Herba Based on Electronic Tongue Technology and Discovery of the Key Compounds of Bitter Substances. *Molecules*, *23*(12), 3362. doi:10.3390/molecules23123362

## Propolis containing ingredients

Bogdanov, S. (2006). Contaminants of bee products. *Apidologie*, 37(1), 1-18. doi: 10.1051/apido:2005043

Sales, A., Alvarez, A., Areal, M. R., Maldonado, L., Marchisio, P., Rodríguez, M. & Bedascarrasbure, E. (2006). The effect of different propolis harvest methods on its lead contents determined by ET AAS and UV–visS. *Journal of Hazardous Materials*, 137(3), 1352–1356. doi:10.1016/j.jhazmat.2006.05.026

WHO (2020). Regulations and controls on lead paint. Global Health Observatory (GHO) data. Accessed September 2020. Available from: https://www.who.int/gho/phe/chemical_safety/lead_paint_regulations/en/

## Caffeine

Southward, K., Rutherfurd-Markwick, K., Badenhorst, C. & Ali, A. (2018), The Role of Genetics in Moderating the Inter-Individual Differences in the Ergogenicity of Caffeine. *Nutrients 10*(10), 1352; doi:10.3390/nu10101352